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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,261	12/03/2003	Herbert W. Harris	18184-0004 US	7783

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EXAMINER	
CARTER, KENDRA D	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,261	HARRIS ET AL.	
	Examiner	Art Unit	
	Kendra D. Carter	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *13-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the Applicant's response on December 29, 2006 to the non-final rejection filed July 27, 2006. Due to a specification objection, a 35 USC 103(a) rejection and an obvious double patenting rejection not made in the previous office action, a new non-final rejection is being made below. The election/restriction is repeated for clarity since this is a new action.

The double patenting rejections of claims 1-12 made in the previous office action filed July 27, 2006 are withdrawn due to the terminal disclaimers disclosed December 29, 2006.

Claims 1-58 are pending in the application. Claims 13-58 are withdrawn from consideration.

Election/Restrictions

From the election restriction dated May 17, 2006, the Applicant elected in the remarks dated June 8, 2006 Group I (claims 1-12) without traverse on the right to obtain rejoinder of all other claims. Therefore, the restriction is upheld and made final.

Specification

The amendment filed December 29, 2003 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the "mg/kg/day" was changed to "mg/day". The specification does not support this change because the examples (see pages 47-49, example 6; specifically page 48, table 3 and page 49, lines 1 and 13-14 and table 4) provided by the Applicant are all in the "mg/kg" measurement that were given in one dose (i.e. per day).

Applicant is required to cancel the new matter in the reply to this Office Action.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 1-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10-14, and 16-20 of copending Application No. 10/578,522.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons below.

The U.S. Application 10/578,522 discloses a method of treating an individual afflicted with an inflammatory disorder or epithelial tissue comprising administering an effective amount of at least one compound according to formula I as a racemic mixture (see claim 10) or as the (R)-enantiomer substantially free of the corresponding (S)-enantiomer (see claim 16), or a pharmaceutically acceptable salt thereof (see claim 1). The compound of formula I wherein R^1 and R^2 are $(C_1\text{-}C_7)$hydrocarbyl, R^{3b}, R^{3c} and R^5 are $O(C_1\text{-}C_7)$hydrocarbyl, R^{3a} is H, and R^4 is OH, corresponds to the applicant's compound 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine. In claims 14 and 20, 10/578,522 discloses a method comprising the applicant's specific compound stated above.

10/578,522 does not disclose a composition of the (S)-enantiomer substantially free of the corresponding (R)-enantiomer of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine and in which the compound is in 85%, 90% or 95% by weight.

To one having ordinary skill in the art would find it obvious to formulate a composition of the (R) or (S)-enantiomer of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine from the method of 10/578,522 because the method of treatment comprises administering the racemic mixture and the (R)-enantiomer of the same compound, thus rendering the composition obvious.

A composition of the (S)-enantiomer is obvious because the racemic mixture and the (R)-enantiomer is taught by 10/578,522. Stereoisomerism is well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have been motivated to resolve the racemic mixture with the reasonable expectation of achieving substantially different pharmacological activity.

The weight percents of the composition would also be obvious because it is the normal desire of scientists or artisans to improve upon what is already generally known. Thus, the composition of the (R) and (S)-enantiomer of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine in 85%, 90% or 95% by weight is taught by 10/578,522.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korosi et al. (US 4,322,346) in view of Ito (Tokyo Ika Daigaku Zasshi, 1981, 39(3), 269-384).

Korosi et al. the applicant's racemic compound as formula I wherein R = phenyl, R^1 = methyl (C_{1-3} alkyl), R^2 = ethyl (C_{1-4} alkyl), R^3 = hydroxyl, and R^4 = methoxy (C_{1-3} alkoxy) or a pharmaceutically acceptable salt on column 1, lines 12-43. The regioisomer of the Applicant's compound wherein 7 is hydroxyl and 8 is methoxy on the benzodiazepine ring on column 8, example 23. The compounds can be converted into pharmaceutical compositions according to methods well known in the art, by admixing them with conventional pharmaceutical carriers, diluents and/or other additives.

Korosi et al. does not teach the specific compound 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine in the specific (R)- or (S)-enantiomer and in which the compound is in 85%, 90% or 95% or more of the total

weight of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine

Ito teaches the regioisomer of the applicant's racemic compound as formula TF 2 wherein 7 is hydroxyl and 8 is methoxy on the benzodiazepine ring (see page 4, Fig. 1). The compound are either suspended in carboxymethylcellulose or dissolved in a mixture of propylene glycol, ethanol and water before being administered orally (see page 2, experimental materials, paragraph 2, lines 1-2 to page 3, lines 1-2, and page 9, paragraph 1, lines 1-2). The structure activity studies found that substituting the methoxy groups in the 7 and/or 8 positions of the 2,3-benzodiazepine ring with a hydroxyl group (see Fig. 1) brought about a decrease in its acute toxicity and had similar effects (see abstract, paragraph 2, lines 3-5 and page 24, conclusions, paragraph 4, lines 1-4). It was also found that the methoxy group at the 7 position of the 2,3-benzodiazipine ring plays the most important role (see page 24, line 2).

To one having ordinary skill in the art would find it obvious to formulate a composition of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine from the composition of Korosi et al. because the compositions comprise the same compound, and specifically the regioisomer of the Applicant's compound wherein 7 is hydroxyl and 8 is methoxy is taught. Additionally, Ito also teaches the regioisomer of the Applicant's compound wherein 7 is hydroxyl and 8 is methoxy, and substituting the methoxy groups in the 7 and/or 8 positions of the 2,3-

benzodiazepine ring with a hydroxyl group (see Fig. 1) brought about a decrease in its acute toxicity and had similar effects (see abstract, paragraph 2, lines 3-5 and page 24, conclusions, paragraph 4, lines 1-4). Structure activity studies showed that the methoxy group at the 7 position of the 2,3-benzodiazipine ring plays the most important role (see page 24, line 2), thus rendering the composition of the Applicant's specific compound obvious.

One would be motivated to formulate a composition with the specific compound 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine for the following reasons: (1) Korosi et al. teaches the general formula of the compound; (2) Korosi et al. teaches the regioisomer of the Applicant's compound wherein 7 is hydroxyl and 8 is methoxy; (3) Ito also teaches the regioisomer of the Applicant's compound wherein 7 is hydroxyl and 8 is methoxy, and that substituting the methoxy groups in the 7 and/or 8 positions of the 2,3-benzodiazepine ring with a hydroxyl group (see Fig. 1) brought about a decrease in its acute toxicity and had similar effects (see abstract, paragraph 2, lines 3-5 and page 24, conclusions, paragraph 4, lines 1-4); and (4) the methoxy group at the 7 position of the 2,3-benzodiazipine ring plays the most important role (see page 24, line 2). A novel useful compound that is isomeric with the prior art compound is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. In re Norris, 179 F.2d 970, 84 U.S.P.Q. 458 (C.C.P.A. 1970).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to formulate a composition of the (R) or (S)-enantiomer of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine because the fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving enatiomers having substantially different pharmacological activity. It is well established that expected beneficial results are evidence of obviousness of a claimed invention just as unexpected beneficial results are evidence of unobviousness. In re Skoll, 523 F.2d 1392, 187 U.S.P.Q. 481 (C.C.P.A. 1975); In re Skoner, 517 F.2d 947, 186 U.S.P.Q. 80 (C.C.P.A. 1975; In re Gershon, 372 F.2d 535, 152 U.S.P.Q. 602 (C.C.P.A. 1967).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to formulate the weight percents of the composition for the following reasons: (1) upon separating the isomers, unless the mixture is 100% pure, percentages of the other enantiomer will be in the mixture, thus resulting in a composition with 85%, 90% or 95% of the desired enantiomer; and (2) it is the normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages. See In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of the result effective

variable in a known process is ordinarily within the skill of the art." See, e.g., In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *In re Paterson* Appeal No. 02-1189 (Fed. Cir. January 8, 2003).

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KDC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER